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<p><b>(21) International Application Number:</b> <b>PCT/US89/03648</b></p> <p><b>(22) International Filing Date:</b> <b>24 August 1989 (24.08.89)</b></p> <p><b>(30) Priority data:</b> 236,828 26 August 1988 (26.08.88) US</p> <p><b>(71) Applicant:</b> ALCON LABORATORIES, INC. [US/US]; 6201 South Freeway, Fort Worth, TX 76134-2099 (US).</p> <p><b>(72) Inventor:</b> CAGLE, Gerald, D. ; 4224 Buttonwood Road, Fort Worth, TX 76133 (US).</p> <p><b>(74) Agent:</b> PRICE, Robert, L.; Lowe, Price, LeBlanc, Becker &amp; Shur, Suite 300, 99 Canal Center Plaza, Alexandria, VA 22314 (US).</p>			<p><b>(81) Designated States:</b> AT (European patent), AU, BE (European patent), CH (European patent), DE (European patent), FR (European patent), GB (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent).</p> <p><b>Published</b> <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>

**(54) Title:** COMBINATION OF QUINOLONE ANTIBIOTICS AND STEROIDS FOR TOPICAL OPHTHALMIC USE

**(57) Abstract**

Disclosed are pharmaceutical compositions containing a quinolone antibiotic, such as ciprofloxacin, and a steroid, such as rimexolone, dexamethasone, fluorometholone or fluorometholone acetate, and the like for topical ophthalmic delivery, and a method of treatment comprising administering said compositions topically to the affected ocular tissue when indicated for control of infection and associated inflammation.

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COMBINATION OF QUINOLONE ANTIBIOTICS AND  
STEROIDS FOR TOPICAL OPHTHALMIC USE

BACKGROUND OF THE INVENTION

The present invention relates to the topical ophthalmic use of antibiotics in combination with anti-inflammatory steroids to treat ophthalmic infections and attendant inflammation of ocular tissue. Such 5 combinations are generally known and commercially available in the ophthalmic pharmaceutical art. However, there are concerns and expressed reservations in the ophthalmic community about the safety and 10 efficacy of such prior art combinations. There is, moreover, a long felt need for effective and safe topical ophthalmic pharmaceutical compositions containing a potent steroid and a broad spectrum antibiotic which, when administrated to the eye when 15 indicated for bacterial infection or as a prophylactic after ophthalmic trauma and injury, will not, as a possible expression of the steroid component, inhibit the activity of the antibiotic or interfere with normal wound healing, but at the same time will control 20 inflammation. Unexpectedly it has been discovered that combinations of broad spectrum quinolone antibiotics such as ciprofloxacin, norfloxacin, oflaxacin, difloxacin, pefloxacin or the like and potent steroids such as dexamethasone, fluorometholone, fluorometholone 25 acetate, prednisolone, prednisolone acetate, medrysone, betamethasone and rimexolone or the like, including pharmaceutically acceptable salts thereof, meet these

**SUBSTITUTE SHEET**

criteria. The foregoing antibiotics and steroids are known. A preferred antibiotic is ciprofloxacin. Preferred steroids include dexamethasone and rimexolone; the latter compound is described in U. S. 5 Patent No. 3,947,478, the entire contents of which are hereby incorporated in the present specification by reference.

#### DETAILED DESCRIPTION OF THE INVENTION

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The compositions of the present invention are administered topically. The dosage range is 0.001 to 5.0 mg/per eye; wherein the cited mass figures present the sum of the two components, e.g. the steroid and the 15 quinolone antibiotic. The compositions of the present invention can be administered as ointments, solutions, suspensions, or emulsions (dispersions) in a suitable ophthalmic vehicle.

In forming compositions for topical administration, the mixtures are preferably formulated 20 as 0.01 to 2.0 percent by weight (figures relate to combined presence of the steroid and quinolone antibiotic) solutions in water at a pH of 4.5 to 8.0., While the precise regimen is left to the discretion of 25 the clinician, it is recommended that the resulting solution be topically applied by placing one drop in each eye two times a day.

Other ingredients which may be desirable to use in 30 the ophthalmic preparations of the present invention include preservatives, co-solvents and viscosity building agents.

##### Antimicrobial Preservative:

Ophthalmic products are typically packaged in multidose form. Preservatives are thus required to

5 prevent microbial contamination during use. Suitable preservatives include: benzalkonium chloride, thimerosal, chlorobutanol, methyl paraben, propyl paraben, phenylethyl alcohol, edetate disodium, sorbic acid, Onamer M, or other agents known to those skilled in the art. Typically such preservatives are employed at a level of from 0.001% to 1.0% by weight.

Co-Solvents:

10 The solubility of the components of the present compositions may be enhanced by a surfactant or other appropriate co-solvent in the composition. Such co-solvents include polysorbate 20, 60, and 80. Pluronic F-68, F-84 and P-103, cyclodextrin, or other agents known to those skilled in the art. Typically such co-solvents are employed at a level of from 0.01% to 2% by weight.

Viscosity Agents:

20 Viscosity increased above that of simple aqueous solutions may be desirable to increase ocular absorption of the active compounds, to decrease variability in dispensing the formulation, to decrease physical separation of components of a suspension or emulsion of the formulation and/or to otherwise improve the ophthalmic formulation. Such viscosity building agents include, for example, polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxy propyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxy propyl cellulose or other agents known to those skilled in the art. Such agents are typically employed at a level of from 0.01% to 2% by weight.

25 30 The following examples are presented to further illustrate representative topical ophthalmic pharmaceutical compositions of the present invention.

Example I

	<u>Ingredient</u>	<u>Amount</u>	<u>Wt. %</u>
5	Dexamethasone, Micronized USP	1.0 mg + 5% excess	0.10% + 5% excess
	Ciprofloxacin, USP	3.0 mg + 5% excess	0.30% + 5% excess
10	Benzalkonium Chloride Solution (10%), NF	0.001 ml + 10% excess	0.10% + 10% excess <sup>1</sup>
	Eddetate Disodium, USP	0.1 mg	0.01%
	Sodium Chloride, USP	3.0 mg	0.3%
	Sodium Sulfate, USP	12.0 mg	1.2%
15	Tyloxapol, USP	0.5 mg	0.05%
	Hydroxyethylcellulose	2.5 mg	0.25%
	Sulfuric Acid and/or		
	Sodium Hydroxide, NF	QS for pH adjustment to 5.5 ± 0.5	
	Purified Water, USP	QS to 1 ml	QS to 100%
20	1 The benzalkonium chloride, NF concentration is equivalent to 0.01% (+ 10% excess).		

Example II

	<u>Ingredient</u>	<u>Amount</u>	<u>Wt. %</u>
25	Fluorometholone Acetate, USP	1 mg + 2% excess	0.1% + 2% excess
	Ciprofloxacin, USP	3 mg + 7% excess	0.3% + 7% excess
30	Chlorobutanol, Anhydrous, NF	5 mg + 15% excess	0.5 % + 25% excess
	Mineral Oil, USP	50 mg	5%
	White Petrolatum, USP	QS 1 g	QS 100%

The invention has been described herein by reference to certain preferred embodiments. However, as obvious variations thereon will become apparent to those skilled in the art, the invention is not to be considered as limited thereto.

Claims

1. An antibiotic/antiinflammatory ophthalmic pharmaceutical composition for topical delivery to the eye, comprising a therapeutically effective amount of an antibiotic selected from ciprofloxacin, norfloxacin, ofloxacin, difloxacin and pefloxacin; a therapeutically effective amount of an antiinflammatory steroid selected from dexamethasone, prednisolone, prednisolone acetate, medrysone, fluormetholone, fluorometholone acetate, rimexolone, and betamethasone; and a pharmaceutically acceptable vehicle therefor.

2. An antibiotic/antiinflammatory ophthalmic pharmaceutical composition according to Claim 1, wherein the ratio of the antibiotic to the steroid is in the range of from 0.1:1.0 to 10.0:1.0.

3. A composition according to Claim 1 wherein the antibiotic comprises ciprofloxacin.

4. A composition according to Claim 1 wherein the steroid is selected from dexamethasone, fluorometholone and rimexolone.

5. A composition according to Claim 1, wherein the antibiotic comprises ciprofloxacin and the steroid is selected from dexamethasone, fluorometholone and rimexolone.

6. A composition according to Claim 1, wherein the antibiotic comprises ciprofloxacin and the steroid comprises rimexolone.

7. A composition according to Claim 1, wherein the antibiotic comprises ciprofloxacin and the steroid comprises dexamethasone.

8. A composition according to Claim 1, wherein the antibiotic comprises ciprofloxacin and the steroid comprises fluorometholone.

9. A method of treating infection and inflammation of ocular tissue which comprises applying an effective amount of a composition according to Claim 1 topically to the affected ocular tissue.

10. A method according to Claim 9, wherein the composition comprises ciprofloxacin and a steroid selected from rimexolone, dexamethasone, and fluorometholone.

11. A method according to Claim 9, wherein the composition comprises ciprofloxacin and rimexolone.

12. A method according to Claim 9, wherein the composition comprises ciprofloxacin and dexamethasone.

13. A method according to Claim 9, wherein the composition comprises ciprofloxacin and fluorometholone.

# INTERNATIONAL SEARCH REPORT

International Application No. PCT/US89/03648

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (if several classification symbols apply, see item 6) According to International Patent Classification (IPC) or to both National Classification and IPC IPC(4): A61K 31/56 U.S.CI.: 514/171													
<b>II. FIELDS SEARCHED</b> <table style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 20%;">Classification System</th> <th style="width: 80%;">Minimum Documentation Searched <sup>7</sup></th> </tr> </thead> <tbody> <tr> <td style="text-align: center;">U.S.</td> <td style="text-align: center;">Classification Symbols 514/171</td> </tr> </tbody> </table>		Classification System	Minimum Documentation Searched <sup>7</sup>	U.S.	Classification Symbols 514/171								
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<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT</b> <sup>9</sup> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 10%;">Category <sup>10</sup></th> <th style="width: 70%;">Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup></th> <th style="width: 20%;">Relevant to Claim No. <sup>13</sup></th> </tr> </thead> <tbody> <tr> <td style="text-align: center;">X</td> <td>US, A 4 474,751 (HASLAM ET AL) 02 October 1984, see column 4, line 57 - column 5 line 14.</td> <td style="text-align: center;">1-13</td> </tr> <tr> <td style="text-align: center;">X</td> <td>US, A 4 730 013 (BONDI ET AL) 08 March 1988 see column 2 line 35 - column 3, line 15.</td> <td style="text-align: center;">1-13</td> </tr> <tr> <td style="text-align: center;">P, X</td> <td>US, A 4 844 902 (GROHE) 04 July 1989, see column 2 line 41 - column 3, line 17</td> <td style="text-align: center;">1-13</td> </tr> </tbody> </table>		Category <sup>10</sup>	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>	X	US, A 4 474,751 (HASLAM ET AL) 02 October 1984, see column 4, line 57 - column 5 line 14.	1-13	X	US, A 4 730 013 (BONDI ET AL) 08 March 1988 see column 2 line 35 - column 3, line 15.	1-13	P, X	US, A 4 844 902 (GROHE) 04 July 1989, see column 2 line 41 - column 3, line 17	1-13
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* Special categories of cited documents: <sup>10</sup> "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed  "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family													
<b>IV. CERTIFICATION</b> <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%;">Date of the Actual Completion of the International Search</td> <td style="width: 50%;">Date of Mailing of this International Search Report</td> </tr> <tr> <td style="text-align: center;">07 NOVEMBER 1989</td> <td style="text-align: center;">10 JAN 1990</td> </tr> <tr> <td>International Searching Authority</td> <td>Signature of Authorized Officer</td> </tr> <tr> <td>ISA/US</td> <td style="text-align: center;"><i>Joseph A. Lipoovsky</i></td> </tr> </table>		Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	07 NOVEMBER 1989	10 JAN 1990	International Searching Authority	Signature of Authorized Officer	ISA/US	<i>Joseph A. Lipoovsky</i>				
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